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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Dario Norberto R. CARRARA et al.	Confirmation No.: 5916
Application No.: 10/798,111	Group Art Unit: 1616
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For: METHODS AND FORMULATIONS FOR TRANSDERMAL OR TRANSMUCOSAL APPLICATION OF ACTIVE AGENTS	Atty. Docket No.: 88066-7900

DECLARATION UNDER 37 C.F.R. § 1.131

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Sir:

I, Dario Carrara, on behalf of my coinventors, Arnaud Grenier, Celine Besse, Stephen M. Simes and Leah M. Lehman, declare that:

1. We are the inventors of the invention described in the above-identified patent application.

2. Attached hereto are pages that describe an invention that was made prior to the March 11, 2002 publication date of WO 02/22132 to Gray et al. ("Gray"). All of the information shown on attached pages was completed prior to March 21, 2002 and disclose various transdermal and transmucosal formulations for administration of active agents using compositions that include a delivery vehicle, permeation enhancers and other components.

3. The paragraph bridging the first two pages lists a number of active agents for use in such compositions and includes many different hormones with the third page listing certain preferred embodiments of such hormones.

4. The fourth page lists a ternary vehicle for the composition that includes the components of an alkanol, propylene glycol and diethylene glycol monoethyl ether or diethylene glycol monomethyl as well as the relative amounts of such components. Various gelling agents and amounts are disclosed in the paragraph bridging pages 4 to 5.

5. The fifth page discloses other additives as well as a topical method for administration these transdermal formulations.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and any patent issuing thereon.

Dated: Nov 03 2010.

Dario Norberto R. CARRARA

The main objective of this invention is to provide a semisolid dosage form, which shows adequate and effective transdermal penetration enhancement for different active drugs.

Accordingly, it is an object of the present invention to provide a skin permeation enhancer composition comprising of a first component that is a saturated fatty alcohol or fatty acid given by the formula CH_3-$(CH_2)_n$-CH_2OH or CH_3-$(CH_2)_n$-CH_2COOH respectively, in which n is an integer from 8 to 22, preferably 8 to 12, most preferably 10 or an unsaturated fatty alcohol or fatty acid given by the formula CH_3-$(C_nH_{2(n-x)})$-OH or CH_3-$(C_nH_{2(n-x)})$-COOH respectively in which n is an integer from 8 to 22; and preferably also a second component that is a monoalkyl ether of diethylene glycol, preferably diethylene glycol monoethyl ether or diethylene glycol monomethyl ether, in a vehicle or carrier composition, integrated by an C_1-C_4 alkanol, preferably ethanol; a polyalcohol, preferably propylene glycol and purified water. The composition may also comprise additional components such as gelling agents, pH regulators, preservatives, flavor agents, saborizants, sweeteners, stabilizers, antioxidants, other solubilizants and the like.

The transdermal delivery system of the present invention comprises:

1. One or more active agents, or a mixture thereof. The term "'drug" or "active drug" or "active agents" or "pharmaceutical active drug" as used to describe the principal active ingredient of the device intends a biologically active compound or mixture compounds that has a therapeutic, prophylactic or other beneficial pharmacological and/or physiological effect on the wearer of the device. Examples of types of drugs are:

a) Hormones: estrogens such as 17 beta -Estradiol, Estradiol, Estradiol Benzoate, Estradiol 17 beta -Cypionate, Estriol, Estrone, Ethynil Estradiol, Mestranol, Moxestrol, Mytatrienediol, Polyestradiol Phosphate, Quinestradiol, Quinestrol, etc; progestogens such as Allylestrenol, Anagestone, Chlormadinone Acetate, Delmadinone Acetate, Demegestone, Desogestrel, Dimethisterone, Dydrogesterone, Ethynilestrenol, Ethisterone, Ethynodiol, Ethynodiol Diacetate, Flurogestone Acetate, Gestodene, Gestonorone Caproate, Haloprogesterone, 17-Hydroxy-16-methylene-progesterone, 17 alpha -Hydroxyprogesterone, 17 alpha -

Hydroxygesterone Caproate, Lynestrenol, Medrogestone, Medroxyprogesterone, Megestrol Acetate, Melengestrol, Norethindrone, Norethindrone Acetate, Norethynodrel, Norgesterone, Norgestimate, Norgestrel, Norgestrienone, 19-Norprogesterone, Norvinisterone, Pentagestrone, Progesterone, Natural Progesterone, Promegestone, Quingestrone, Trengestone, etc; androgens such as Fluoxymesterone, Testosterone, Testosterone derivatives such as: 17-Methyltestosterone, Testosterone 17 beta -Cypionate, Testosterone Enanthate, Testosterone Nicotinate, Testosterone Pheynylacetate, Testosterone Propionate, etc.

b) Sedatives and anxyolitics for instance Benzodiazepine derivatives such as Alprazolam, Bromazepam, Flutazolam, Ketazolam, Lorazepam, Prazepam, etc; Amides such as Butoctamide, Diethylbromoacetamide, Ibrotamide, Isovaleryl Diethylamide, Niaprazine, Tricetamide, Trimetozine, Zolpidem, Zopiclone, etc; Arylpiperazines such as Buspirone, etc.

c) Antihypothyroids such as Levothyroxine, Thyroid, Thyroxine, etc.

d) Antihypertensives for instance Benzothiadiazine Derivatives such as Captopril, Cilazapril, Enalapril, Lisinopril, Perindopril, Ramipril; Guanidine Derivatives such as Guanethidine; Quinazoline Derivatives such as Alfuzosin; Reserpine Derivatives such as Reserpine, Sulfonamide Derivatives such as Furosemide; others such as Minoxidil, Amlodipine, Doxazosin Mesylate, Felodipine, Moxonidine, Nicardipine Hydrochloride, Nifedipine, Prazosin hydrochloride, etc and Calcium Channel Blockers such as Arylalkylamines such as Bepridil, Ditiazem, Fendiline, Gallopamil, Terodiline, Verapamil; Dihydropyridine Derivatives such as Felodipine, Isradipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, Nitrendipine, Piperazine; Derivatives such as Flunarisine; others such as Perhexiline Calcium Regulator such as Calcifediol, Calcitonin, Calcitriol, Clodronic Acid, Dihydrotachysterol, Elcatonin, Etidronic Acid, Ipriflavone, Pamidronic Acid, Parathyroid Hormone, Teriparatide Acetate, etc.

The present invention could be applied to other groups of pharmaceutical active agents for instance for alpha –Adrenergic Agonists such as Budralazine, Clonidine, Epinephrine, Fenoxazoline, Naphazoline, Phenylephrine, Phenylpropanolamine, beta –Adrenergic Agonists such as Formoterol, Methoxyphenamine, alpha –Adrenergic Blockers such as Doxazosin, Prazosin,

Terazosin, Trimazosin, Yohimbine, beta -Adrenergic Blockers such as Atenolol, Bisoprolol, Carteolol, Carvedilol, Metoprolol, Nadolol, Penbutolol, Analgesics (Narcotics) such as Buprenorphine, Dihydromorphine, Metazocine, Methadone, Morphine, Morphine Derivatives, Nicomorphine, Oxymorphone, etc.; Nerve Agents for smoking cessation i.e. such as Nicotine, Nicotine Citrate and Nicotine Tartrate, Antineoplastic Agents such as 5-Fluorouracil, etc; Analgesics (Non-Narcotics), Analgesic and Anti-Inflamatory Agents; Anesthetics; Antiandrogens; Antianginals; Anticholinergics; Anticonvulsants; Antidepressants; Antiepileptics; Antiestrogen such as Tamoxifen, 4-OH Tamoxifen; Antihistaminics; Antiparkinsonians; Bronchodilators; Diuretics; Glucocorticoids; Muscle Relaxants; Narcotic Antagonists; etc.

It is to be understood herein that the active agent is intended to mean a single active agent or a combination of more than one active agent.

The amount of the systemically and/or topically active agent included in the formulation is subject to the degree to which penetration enhancement is achieved.

In the preferred embodiments, the active agents are: Testosterone presented in the compositions in about 0.05 to about 10.0 %w/w; preferably from about 0.1 to about 5.0 %w/w and more preferably 0.6 to 4.0 %w/w. Estradiol presented in the compositions in about 0.02 to about 3.0 %w/w; preferably from about 0.04 to 2.0 %w/w and more preferably 0.06 to 0.12 %w/w. Ethynil Estradiol presented in the compositions in about 0.02 to about 3.0 %w/w; preferably from about 0.04 to 0.5 %w/w and more preferably 0.06 to 0.12 %w/w. Levonorgestrel presented in the compositions in about 0.02 to about 3.0 %w/w; preferably from about 0.04 to 0.5 %w/w and more preferably 0.06 to 0.12 %w/w. Progesterone presented in the compositions in about 0.1 to about 10.0 %w/w; preferably from about 0.1 to 5.0 %w/w and more preferably 1.0 to 3.0 %w/w. Alprazolam presented in the compositions in about 0.02 to about 6.0 %w/w; preferably from about 0.1 to 3.0 %w/w and more preferably 0.5 to 2.0 %w/w. L-Thyroxine presented in the compositions in about 0.02 to about 4.0 %w/w; preferably from about 0.04 to 2.0 %w/w and more preferably 0.2 to 1.0 %w/w. Amlodipine or Amlodipine Besylate presented in the compositions in about 0.05 to about 5.0 %w/w; preferably from about 0.2 to 3.0 %w/w and more preferably 0.5 to 2.0 %w/w.

2. A ternary vehicle composite comprised of a C_2-C_4 alkanol such as ethanol, isopropanol, n-propanol, butanol, preferably ethanol; a polyalcohol or glycol such as propylene glycol, butylene glycol, hexylene glycol, ethylene glycol, preferably propylene glycol and finally purified water. The compositions in accordance with the present invention contain an alcohol, preferably ethanol, in an amount of about 5.0 to about 75.0 %w/w; preferably from about 15.0 % to about 65.0 %w/w and more preferably 20.0 to 55.0 %w/w. In addition, the compositions of the present invention comprises a glycol, preferably propylene glycol in about 0.5 to about 50.0 %w/w; preferably from about 3.0 to 20.0 %w/w and more preferably 4.0 to 10.0 %w/w.

3. A permeation enhancer system comprising of a first component that is a saturated fatty alcohol or fatty acid given by the formula CH_3-$(CH_2)_n$-CH_2OH or CH_3-$(CH_2)_n$-CH_2COOH respectively, in which n is an integer from 8 to 22, preferably 8 to 12, most preferably 10 or an unsaturated fatty alcohol or fatty acid given by the formula CH_3-$(C_nH_{2(n-x)})$-OH or CH_3-$(C_nH_{2(n-x)})$-COOH respectively in which n is an integer from 8 to 22; and preferably also a second component that is a monoalkyl ether of diethylene glycol, preferably diethylene glycol monoethyl ether or diethylene glycol monomethyl. The compositions in accordance with the present invention contain a fatty alcohol, preferably lauryl alcohol or dodecanol in about 0.1 to about 20.0 %w/w on the whole composition; preferably form about 0.4 to 10.0 %w/w and more preferably 0.2 to 3.0 %w/w; and, optionally, a diethylene glycol monoalkyl ether in amount up to 40.0 %w/w; preferably from about 0.2 to 25.0 %w/w and more preferably 2.0 to 8.0 %w/w.

4. A gelling agent or viscosant, e.g. carbomer, carboxyethylene or polyacrylic acid such as Carbopol 980 or 940 NF, 981 or 941 NF, 1382 or 1342 NF, 5984 or 934 NF, ETD 2020, 2050, 934P NF, 971P NF, 974P NF, Noveon AA-1 USP, etc; cellulose derivatives such as ethylcellulose, hydroxypropylmethylcellulose (HPMC), ethyl-hydroxyethylcellulose (EHEC), carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC) (Klucel different grades), hydroxyethylcellulose (HEC) (Natrosol grades), HPMCP 55, Methocel grades, etc; natural gums such as arabic, xanthan, guar gums, alginates, etc; polyvinylpyrrolidone derivatives such as Kollidon grades; polyoxyethylene polyoxypropylene copolymers such as Lutrol F grades 68, 127, etc; others like chitosan, polyvinyl alcohols, pectins, veegun grades,

etc. In the present invention, Lutrol F grades and Carbopol grades were preferred. Those of the skill in the art should know of other gelling agents or viscosants that are suitable to practice the present invention. Suitable gelling agents to apply the present invention include, but are not limited to, Carbopol 980 NF, Lutrol F 127, Lutrol F 68 and Noveon AA-1 USP. The gelling agent is present from about 0.2 to about 30.0 %w/w depending on the type of polymer.

5. A pH regulator, normally a neutralizant agent, which can optionally have crosslinking function e.g. a ternary amine such as triethanolamine, tromethamine, tetrahydroxypropylethylendiamine, etc; NaOH solution, etc. The pH regulator is present in the formulations in about 0.05 to about 2.0 %w/w.

6. Other ingredients can optionally be included, for example, preservatives and/or antioxidants such as buthylhydroxytoluene, buthylhydroxyanisole, ethylenediaminetetraacetic acid and its sodium salts, DL-alfa tocoferol, antioxidant complexes, etc; co-solvents or solubilizers such as glycerol, polyethylene glycols, polyethylene glycols derivatives, polyethyleneglycol 660 hydroxystearate (Solutol HS15 from Basf), buthylene glycol, hexylene glycol, etc.

The formulations in which the present invention could be added, assume any of a variety of dosage forms. Examples are gels, creams, lotions, sprays, ointments, aerosols, patches, buccal and sublingual tablets, suppositories, vaginal dosage forms and different passive or/and active transdermal devices for absorption through the skin or mucosa.

As such, in another aspect, the present invention relates to a method for administering topically or systemically active agent(s), comprising: 1. An active agent(s); 2. A ternary vehicle composite (composed by a C1-C4 alkanol, a glycol and water); 3. A penetration enhancers combination (fatty alcohol or acid and diethylene glycol monoethyl ether); 4. A gelling agent and 5. A pH regulator.

It has been discovered that in a transdermal formulation comprising different group of drugs as active agents; lauryl alcohol and diethylene glycol monoethyl ether as penetration enhancers, in a ternary vehicle composite comprised of ethanol, propylene glycol and purified water, using a polymer or copolymer of acrylic acid, preferably a carbomer as gelling forming, provides therapeutically effective serum concentration of each active agent throughout at least a 24 hours period. As it is